# Medicinal Chemistry

## Chapter 17

# ANTIDEPRESSANT



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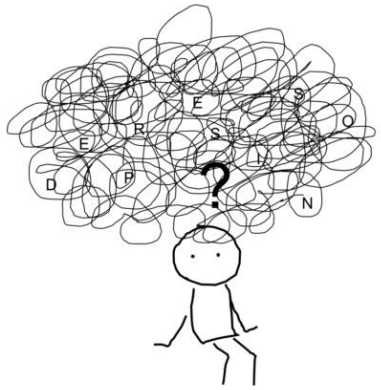
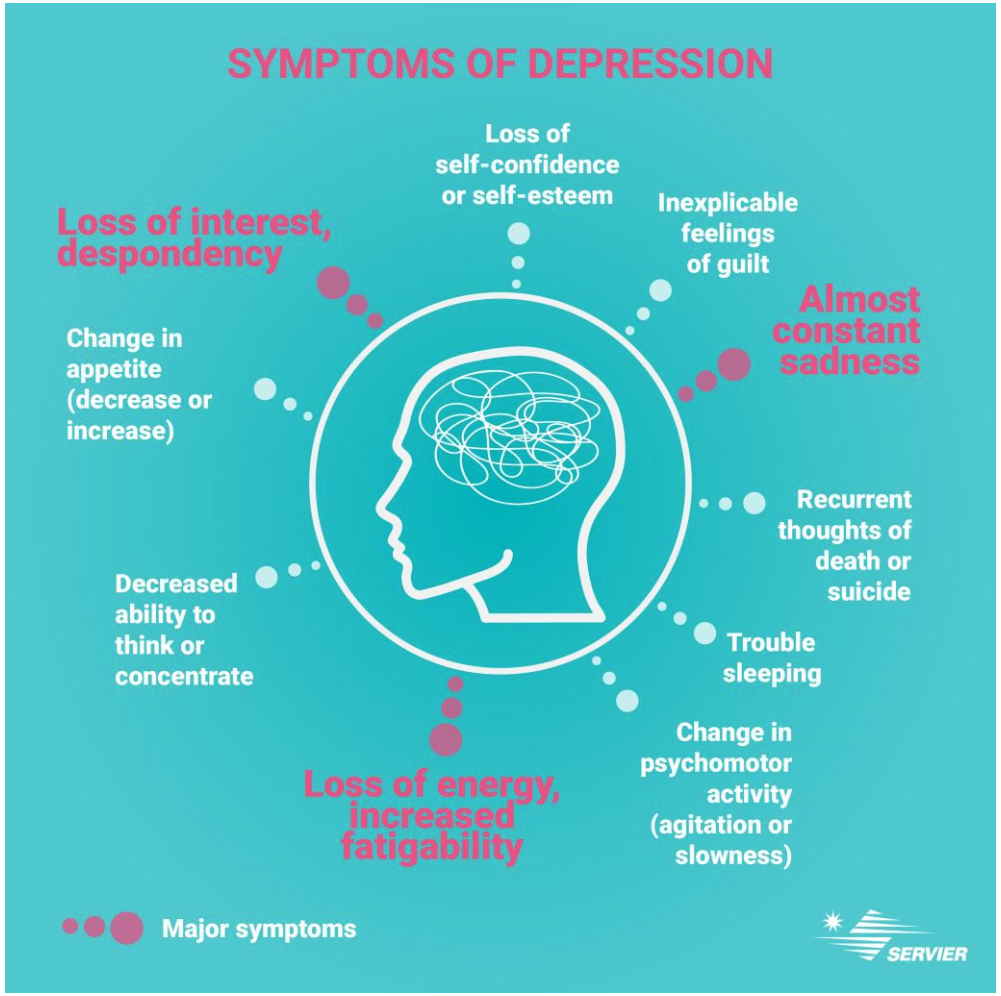
# Contents

# Introduction

- Depression is a common and serious medical illness that negatively affects how you feel, the way you think and how you act.
- Symptoms of depression:
  - Depressed mood most of the day, nearly every day.
  - Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day.
  - Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day.
  - Fatigue or loss of energy nearly every day



- A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down).
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.



# Diagnosis

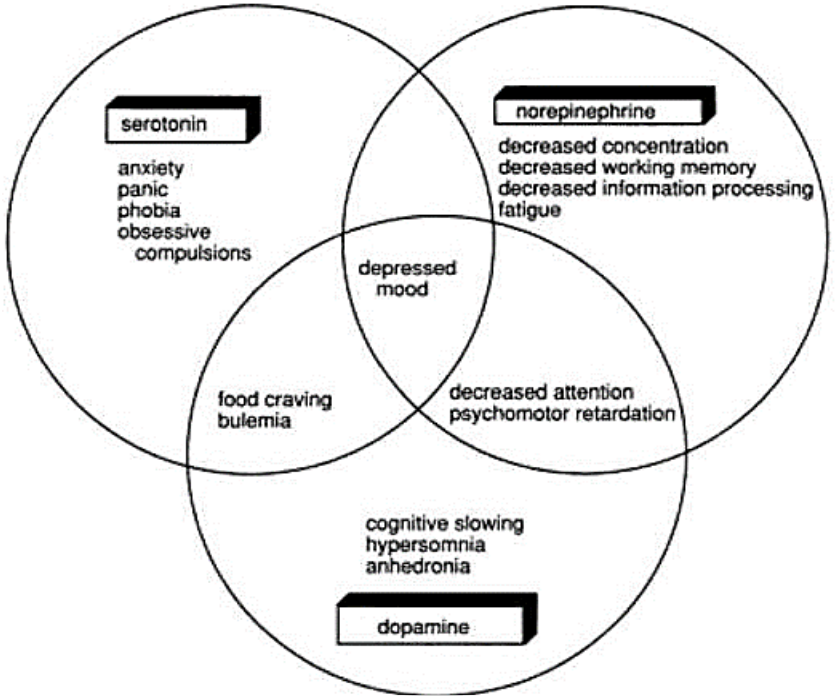
- **Physical exam:** The doctor may do a physical exam and ask questions about your health. In some cases, depression may be linked to an underlying physical health problem.
- **Lab tests:** For example, your doctor may do a blood test called a complete blood count or test your thyroid to make sure it's functioning properly.
- **Psychiatric evaluation:** Your mental health professional asks about your symptoms, thoughts, feelings and behavior patterns. You may be asked to fill out a questionnaire to help answer these questions.
- **DSM-5:** Your mental health professional may use the criteria for depression listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association.
- CT scan or MRI of the brain to rule out serious illnesses such as a brain tumor

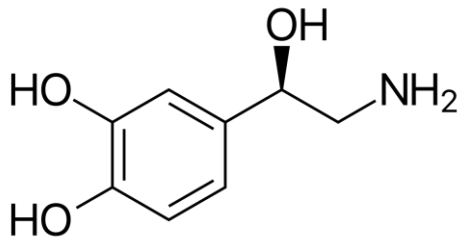
# Cause of Depression

**1- <u>Monoamine Hypothesis :</u>** The accepted cause is deficiency of Neurotransmission by biological amines Nor-adrenaline (NE) and Dopamine (DA) and Serotonin (5HT) in the CNS.

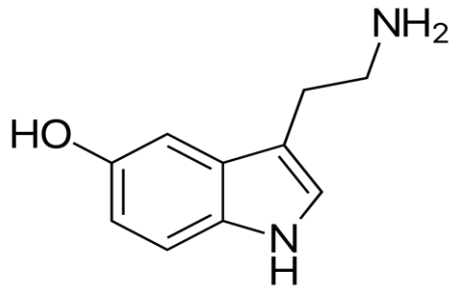
**2- <u>Receptor Sensitivity Hypothesis:</u>** To compensate the deficiency of NE and 5HT in the synapse, the post synaptic receptors become hypersensitive to these neurotransmitters and also they increase in number.

**<u>3- Genetical</u>**




Nor-adrenaline (NE)




Serotonin (5HT)

## Classification of Depressive disorders

- Unipolar: Depression that occurs in a person who never experiences manic highs
- Bipolar: Depression that occurs in a person who sometimes also experiences manic highs
- Reactive: Depression that is supposedly caused by an obvious traumatic life event, like death of a family member or dismissal from a job.
- Endogenous: depression occurs due to the presence of an internal (cognitive, biological) stressor instead of an external (social, environmental) stressor.
- Primary: Depression that is unaccompanied by other psychiatric illness.
- Secondary: Depression that occurs after the onset of another illness, like alcoholism, drug dependency, or medical illness.

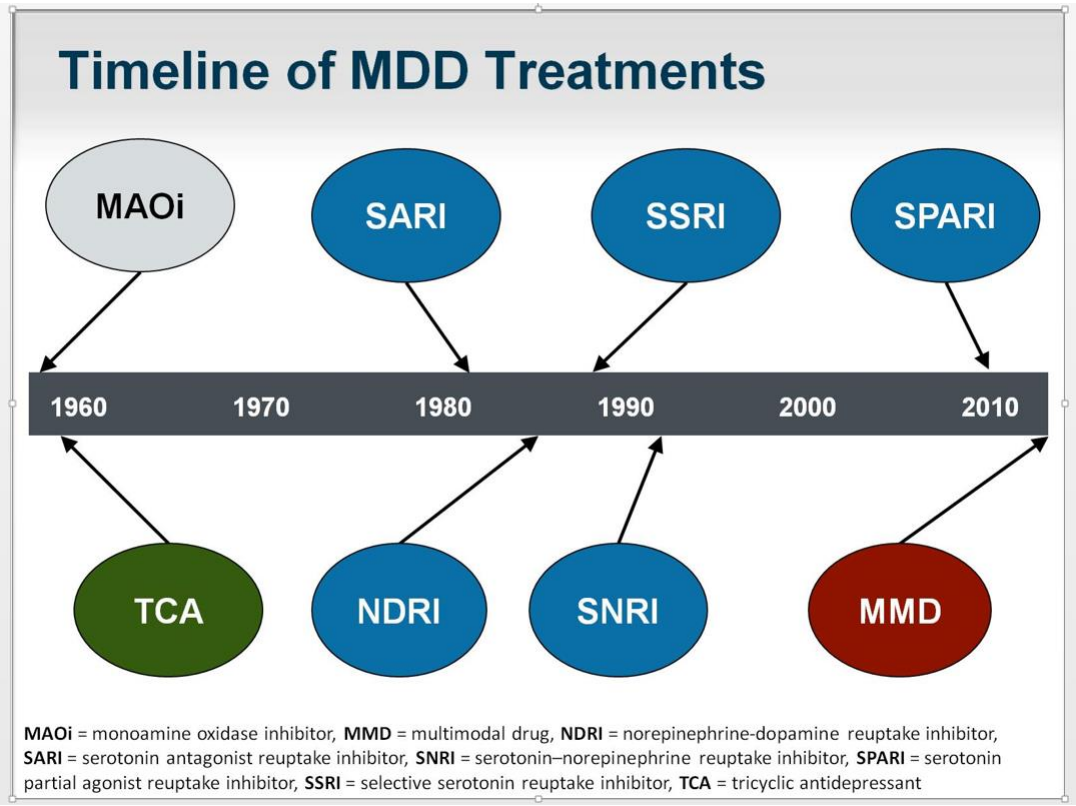
- Atypical: Depression characterized by an ability to be cheered up by some things.
- Major:  Depression characterized by an inability to be cheered up.
- Postpartum: Depression that occurs in a women who has recently had a baby, generally the same as major depression.
- Involutional: Depression that occurs in an elderly person, generally the same as major depression.
- Dysthymia: Low-grade, chronic depression.
- Psychotic: Depression accompanied by hallucinations and/or delusions.
- A person can suffer from several forms of depression at the same time

LET US SEE THIS VIDEO TOGETHER: https://www.youtube.com/watch?v=fWFuQR_Wt4M

# History

- Before 1950, there were no antidepressants, opioids and amphetamines were commonly used in treatment, their use was later restricted due to their addictive nature and side effects.

- At late 1950s was the first generation of antidepressants discovered (the TCAs and MAOIs) by chance after the Second World War, while developing new anti-tuberculosis agents, were the first ones, isoniazid and iproniazid.



- In 1952, the Cincinnati psychiatrist Max Lurie tried it on his patients. In the following year, he and Harry Salzer reported that isoniazid improved depression in two thirds of their patients.
- Imipramine was recognized by Kuhn for its antidepressant properties while searching for "chlorpromazine-like" compounds to treat schizophreia.
- 1970s, the first SSRI  Zimeldine was discovered from the antihistaminic drug Pheniramine since it was also a selective inhibitor of 5HT transporter without any cardio toxic effects
- Zimeldine was withdrawn from market due to Gullain Barre symptom (immune system attacking nerves)

# Targets of antidepressants

- **Monoamine neurotransmitter receptors**
  - Adrenergic receptors
  - Dopamine receptors
  - Histamine receptors
  - Serotonin receptors

- **Monoamine reuptake transporters**
  - Dopamine transporter (DAT)
  - Norepinephrine transporter (NET)
  - Serotonin transporter (SERT)
- **Glutamate receptors**
- **GABA receptors, transporters**

# Antidepressants Classification

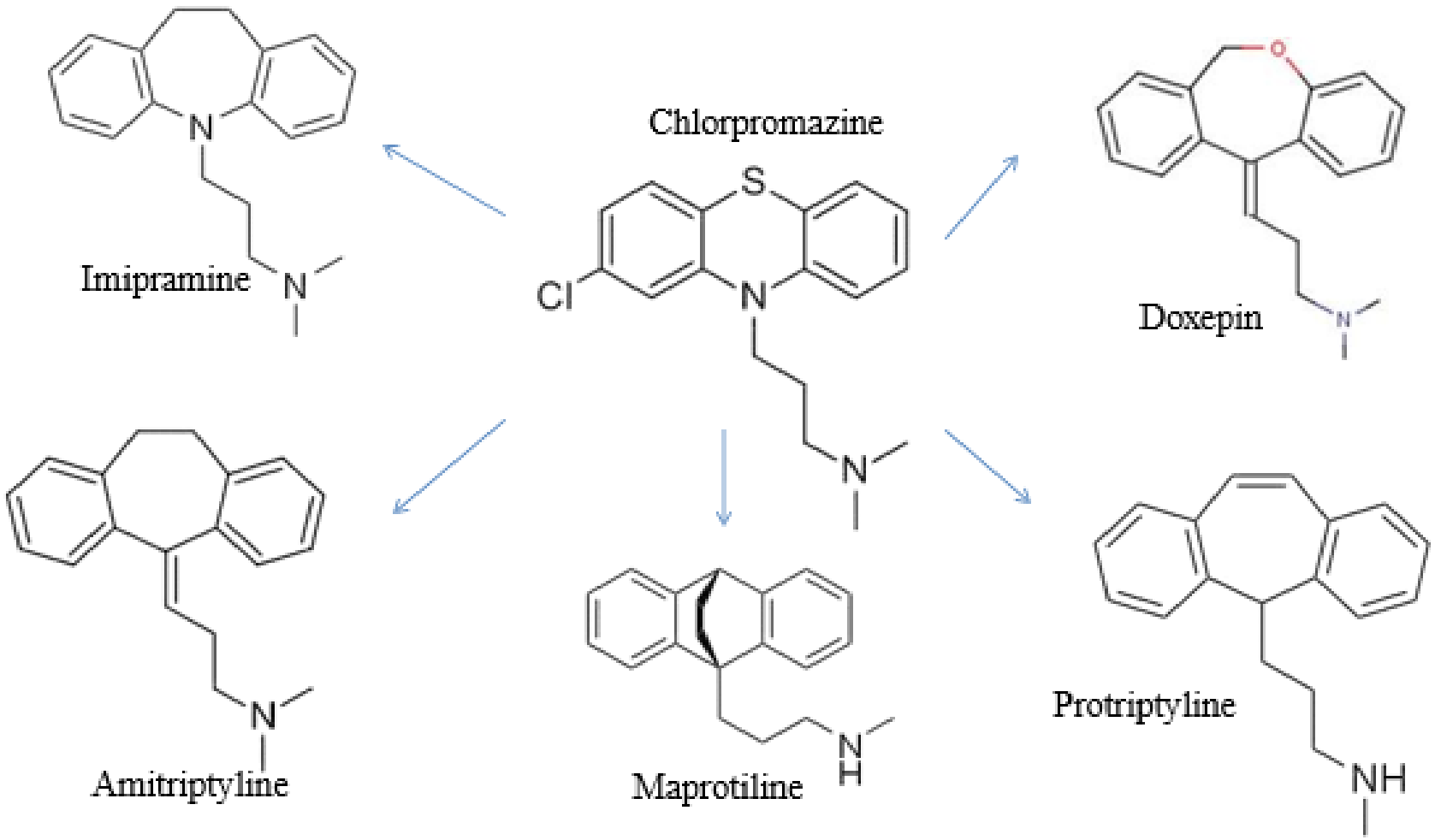
## ❖First-generation

1. *Tricyclics and Tetracyclics (TCA)*
   **Imipramine, Doxepin, Amoxepine.**
2. *Monoamine oxidase inhibitors (MAOIs)*
   **Phenelzine, Moclobemide**

## ❖Second-generation

3. *Selective Serotonin Reuptake Inhibitors (SSRIs)*
   **Fluoxetine, Sertraline, Citalopram**
4. *Serotonin-norepinephrine reuptake inhibitors (SNRIs)*
   **Venlafaxine**
5. *Atypical antidepressants*
   **Bupropion**

## Tricyclic antidepressants (TCAs)

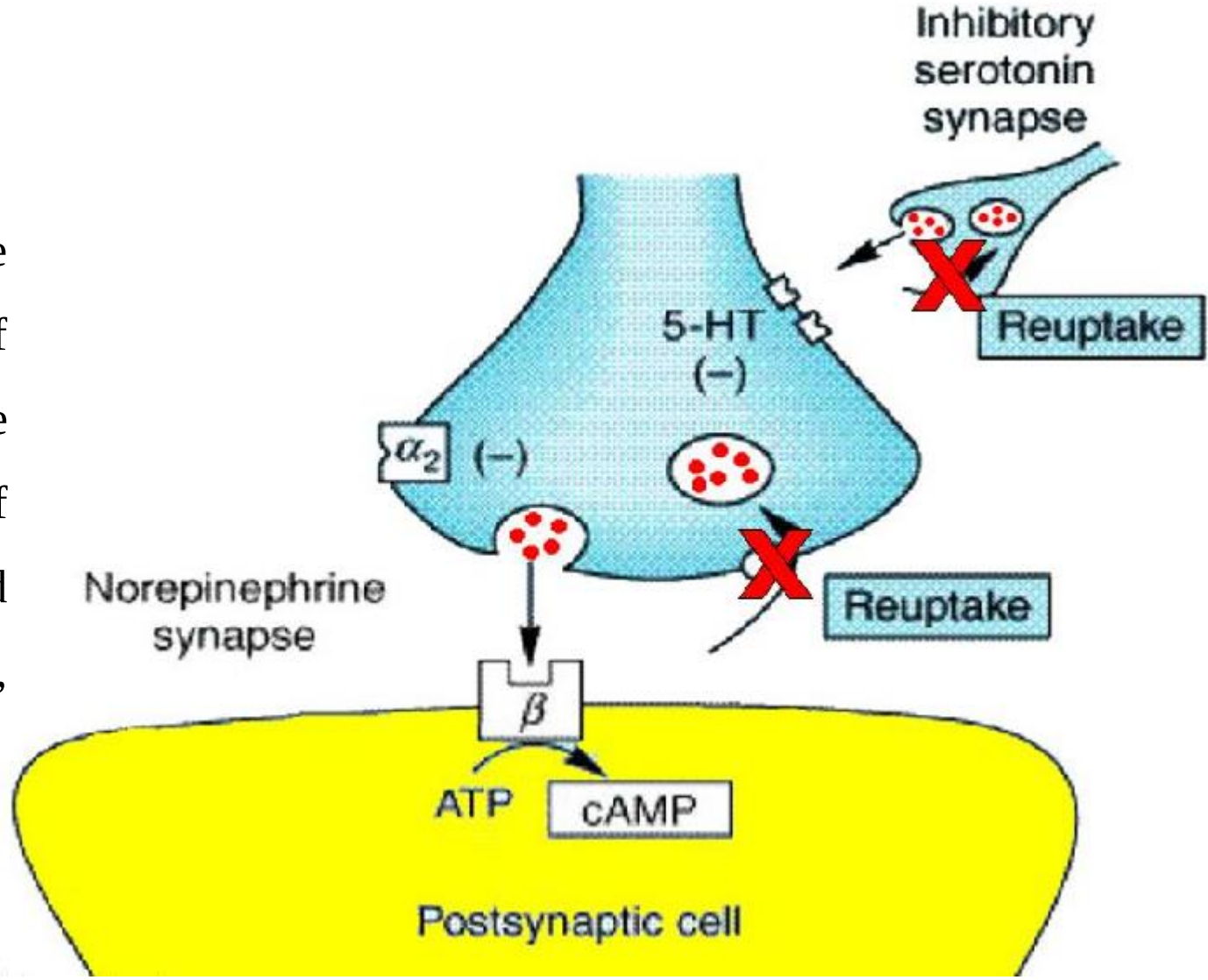



Named because there are three rings in the chemical structure of these medications. They are used to treat depression, fibromyalgia, some types of anxiety, and they can help control chronic pain

These agents work by increasing the levels of norepinephrine and serotonin by preventing their neuronal reuptake, extended duration of post-synaptic effects

## Mechanism of action

Inhibition of neurotransmitter reuptake: TCAs are potent inhibitors of neuronal reuptake of norepinephrine and serotonin into presynaptic nerve terminals ◦ By blocking the major route of neurotransmitter removal, TCAs cause increased concentrations of monoamines in the synaptic cleft, resulting in antidepressant effects



## TCA- Clinical uses

USES of TCAs Tricyclic antidepressants are approved by the Food and Drug Administration (FDA) for treating

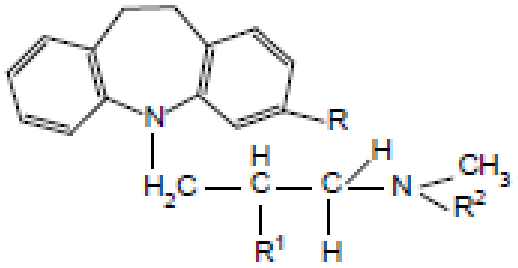
- several types of depression, (Primary drug for depression)
- obsessive compulsive disorder, (NOTE- SSRIs primarily used in this state)
- Bedwetting (nocturnal enurasis) Imipramine at low dose(50mg)

In addition, they are used for several off-label (non-FDA approved) uses such as:

- panic disorder,
- bulimia,
- chronic pain (for example, migraine, tension headaches, diabetic neuropathy, and post herpetic neuralgia), phantom limb pain, chronic itching, and premenstrual symptoms.

## TCAs Classifications:

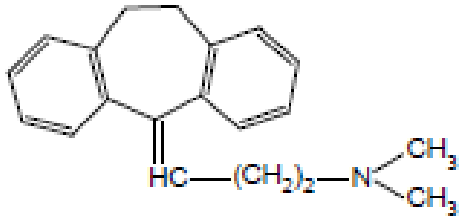
### 1. Imino dibenzyl derivatives



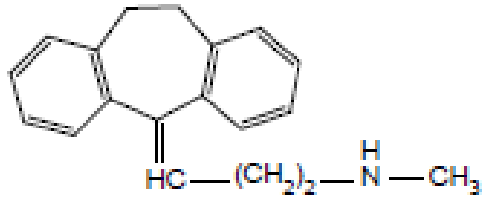
| S. No. | Drugs | R | $R^1$ | $R^2$ |
|---|---|---|---|---|
| 1. | Imipramine | –H | –H | $–CH_3$ |
| 2. | Desipramine | –H | –H | –H |
| 3. | Trimipramine | –H | $–CH_3$ | $–CH_3$ |
| 4. | Chlorimipramine | –Cl | –H | $–CH_3$ |

### 2. Dibenzo cycloheptane derivatives

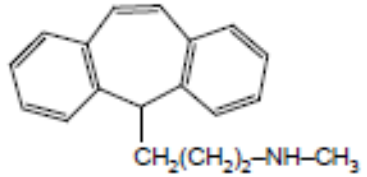
a. Amitryptyline



b. Nortryptyline

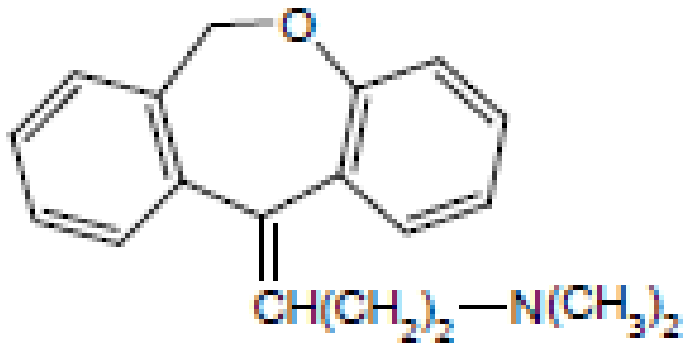


c. Protriptyline

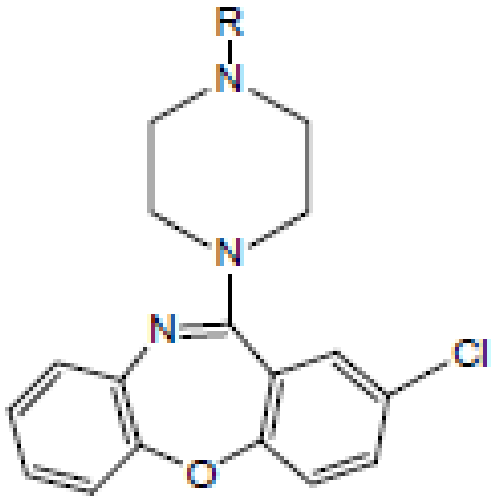


## 3. Dibenzoxepine derivatives

a. Doxepin




## 4. Dibenzoxazepine derivatives

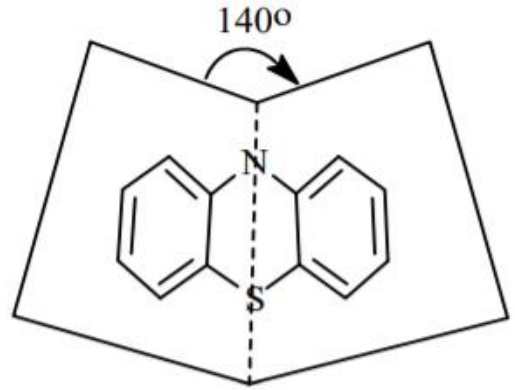



a. Amoxapine R = H

b. Loxapine R–$CH_3$

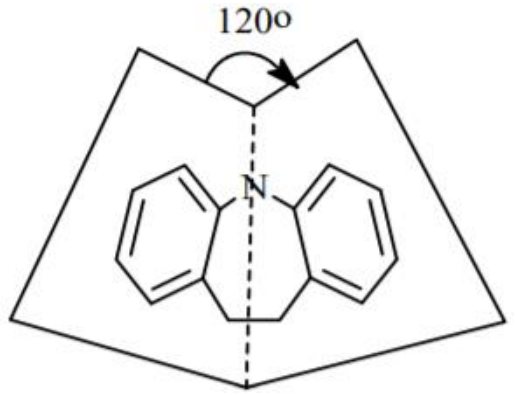
## Structure Activity Relationship of TCAs

1. **General structure:** The tricyclic ring structure is formed by joining the two phenyl rings into 6-6-6 or 6-7-6 ring systems, in which the central ring is either a six-membered or seven-membered carbocyclic or heterocyclic ring, respectively, and a three or sometimes two atom chain bonded to a aliphatic amino group that is monomethyl or dimethyl substituted.



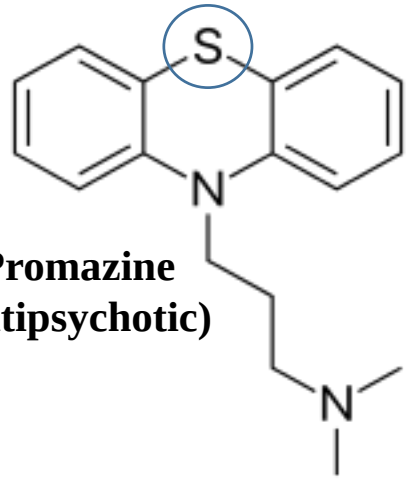

Phenothiazines

- Have similar structures to antipsychotic phenothiazines. However as the **angle between the tricyclic rings are different they have different activities**, since the central ring of the TCAs is made of 7 or 8 atoms, which enables the molecule to bend more and have a smaller angle relative to phenothiazines.

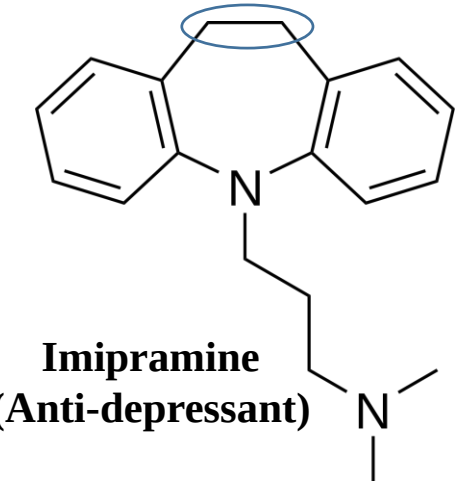



Dibenzazepine (Antidepressant)

- Aslo TCAs differ structurally from the antipsychotic phenothiazines in that the two phenyl (aromatic) rings are connected by a two-carbon link to form a central seven membered ring instead of a sulfur bridge.



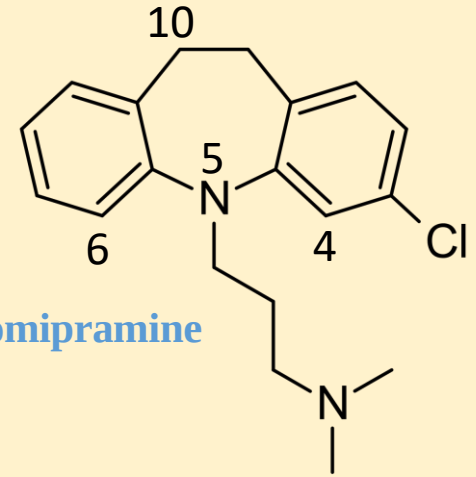

**Promazine (antipsychotic)**




**Imipramine (Anti-depressant)**

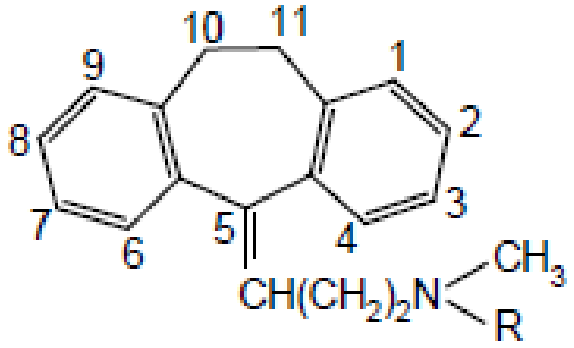
**2. The three rings** do not contribute to receptor binding but are responsible for various CNS side effects due to high lipophilicity. Thus this feature is removed in later inhibitors

- Substituting a halogen or CN (cyano) group in 3 position of either phenyl ring increase selectivity for 5HT transportor
- Presence of dimethyl or keto at C-10 leads to the compounds becoming ineffective.



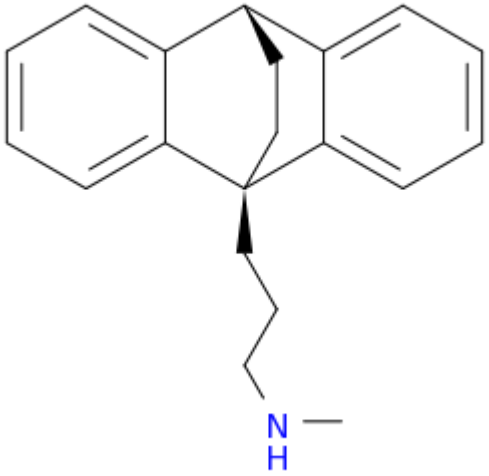

**Clomipramine**

- Presence of double bond between 10 and 11 positions increases the activity.
- When central ring size increases from 7 to 8 members, it is more effective.



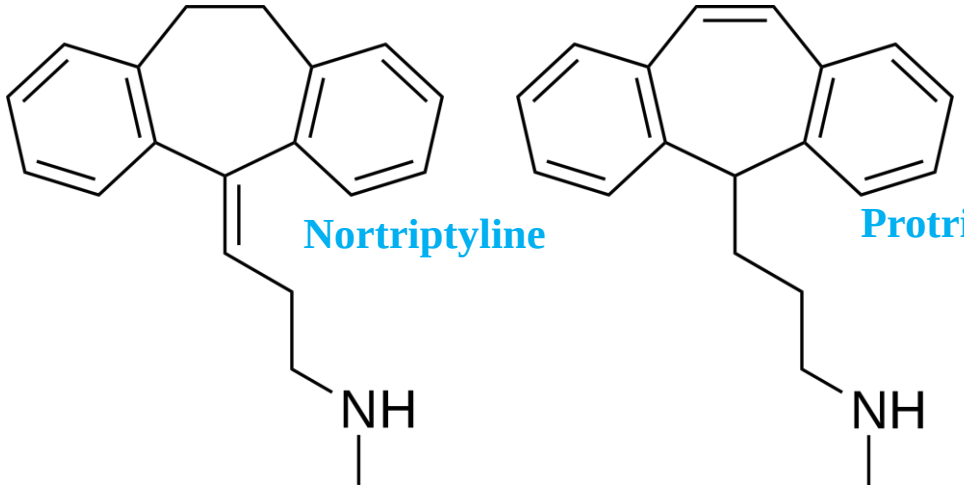

- Several amitriptyline analogues in which replacement of C-11 with O, S, SO, SO2, and NH are clinically effective antidepressants.

- Novel bridged derivatives are very powerful, for example, maprotiline is a potent antidepressant, and the time to steady-state concentration is up to 7 days.



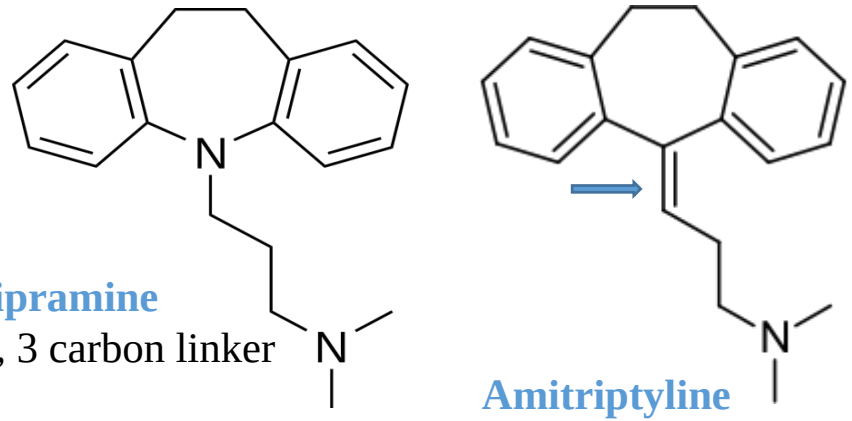

**Maprotiline**

- Nortriptyline with exocyclic double bond and protriptyline with endocyclic double bond differ in their metabolism patterns. Protriptyline is less metabolized in vitro leading to a prolonged half-life and lower dose requirement.




**Nortriptyline** **Protriptyline**

**3. Side chain** of Antidepressants are made up of 3 carbon atoms, in some compounds side chain has 2 carbon atoms. It can be saturated or unsaturated. Unsaturation at C-5 enhances activity.

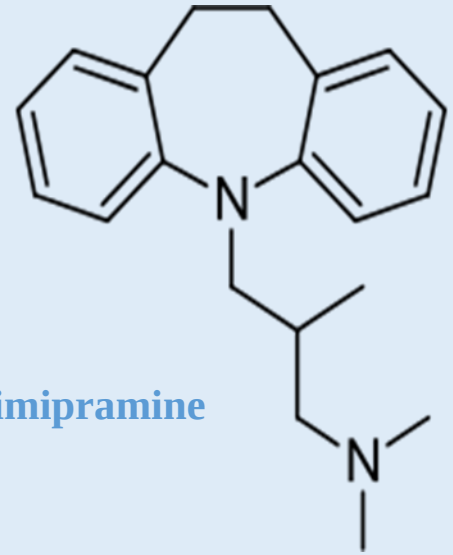



**Imipramine**
Saturated, 3 carbon linker

**Amitriptyline**
Unsaturated, 3 carbon linker

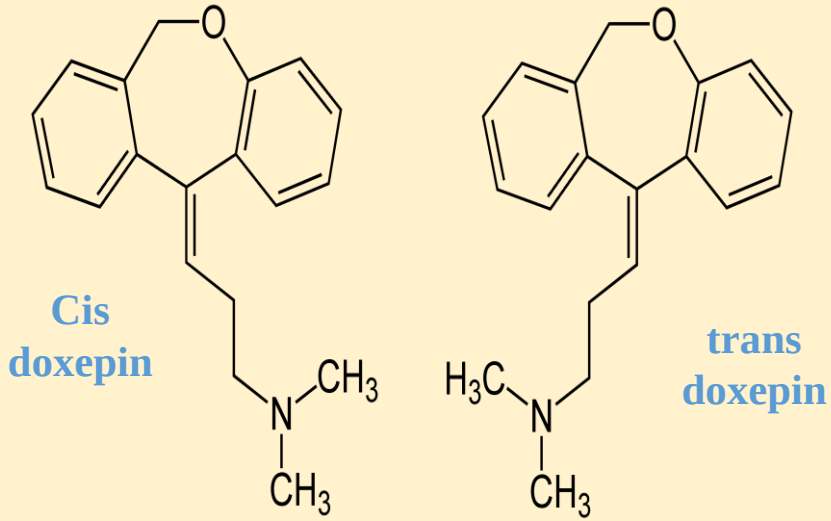
- Increase in the ‘C’ length from propylene leads to it becoming ineffective or produce toxic effects.

Branching reduces potency of Trimipramine by 100 times relative to Imipramine




Trimipramine

Cis form is more potent than trans

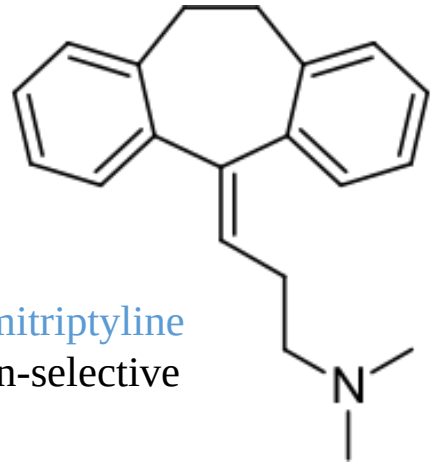



Cis doxepin

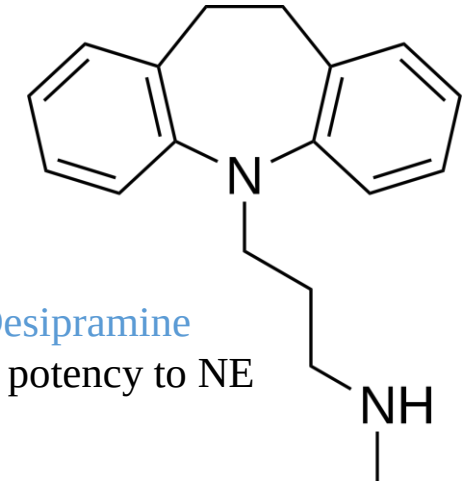
trans doxepin

4. **Amino group** is tertiary or secondary,

- Secondary amine group have more potency to NE transporters,
- Tertiary amine group are non-selective to NE or 5HT transporter's.
- Substituents larger than methyl such as ethyl reduce activity and increases toxicity
- Tertiary amines also have more potent activity to α1 adrenergic, muscarnic, and histaminic receptors.




Amitriptyline
non-selective




Desipramine
more potency to NE

## TCA Side effects

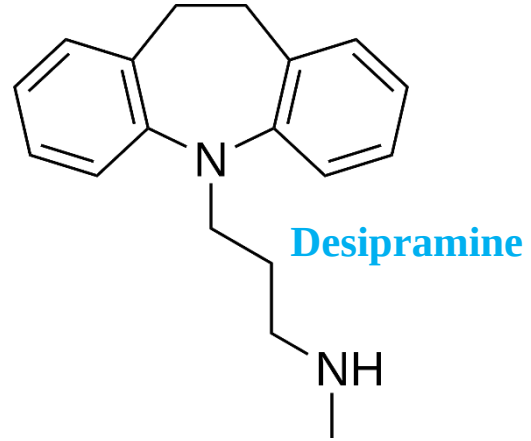
- Dry mouth ,constipation, urinary retention, blurred vision, and confusion
- Life-threatening arrhythmias: The TCAs are class 1A antiarrhythmic agents
- Sedation (H1 antagonism)
- weight gain
- Sexual dysfunction
- At therapeutic doses, the TCA drugs lower the seizure threshold and at toxic doses can cause life-threatening seizures (especially Maprotiline)
- Amoxapine has dopamine receptor antagonist properties and can induce EPS, gynecomastia, lactation, and neuroleptic malignant syndrome

## Imipramine

It is used in the treatment of

- Depression & Bedwetting

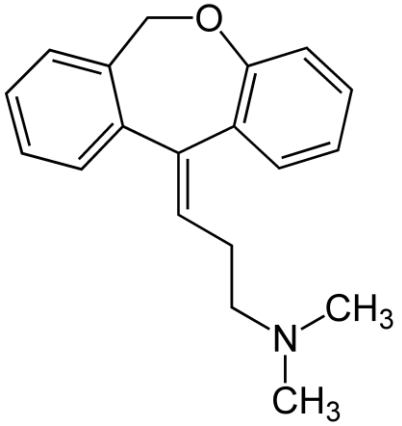
Within the body, Imipramine is demethylated to desipramine



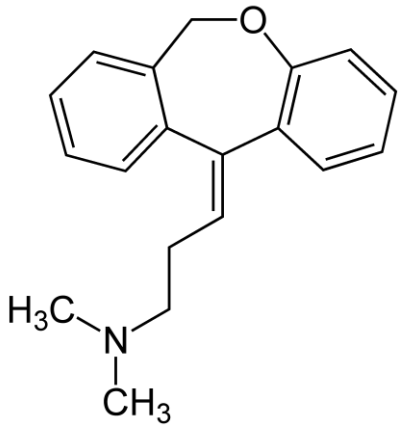

Desipramine

## Doxepin

- Dibenzoxepine group, central ring containing oxygen
- Two isomers are possible and is marketed in 85:15 mixture of Trans : Cis
- Cis form inhibits reuptake of 5HT and Trans form inhibits reuptake of NE

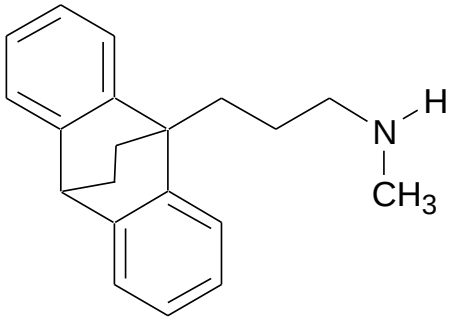



Cis Doxepin

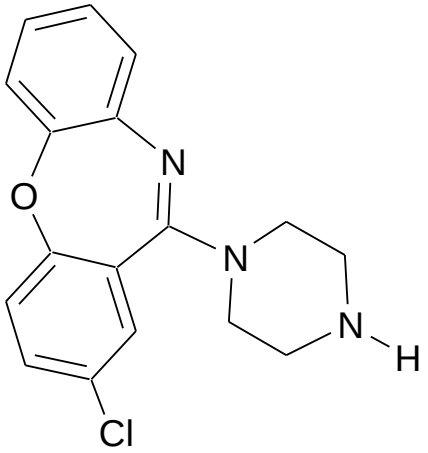



Trans Doxepin

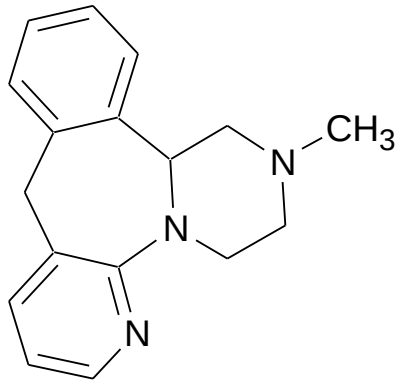
# Miscellaneous Tricyclic Compounds




**Maprotiline:** The ethyl bridge forms a fourth ring (tetracyclic) resulting in skewing of the phenyl rings similar to the TCA's



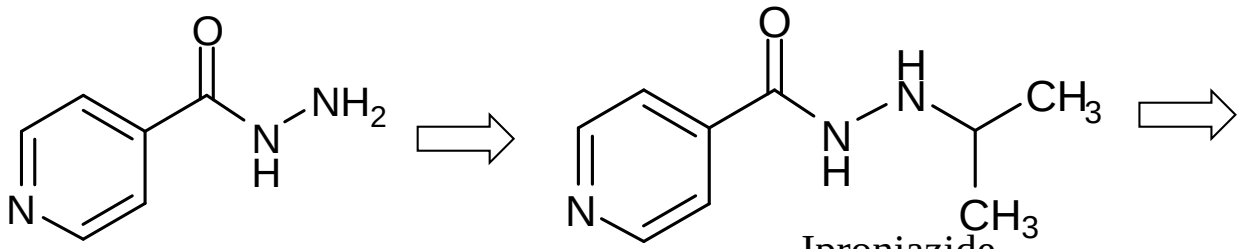

**Amoxapine:** Related to dibenzoxazepine antipsychotic loxapine without *para* methyl group which has been used in depressed psychotics with some success. Has more dopamine antagonistsic activity than some of the other antidepressants. Loxapine, interestingly, has little to no antidepressant activity




**Mirtazapine:** a dibenzazepine but mechanistically is not related to the TCA's at all. It is thought to be presynaptic $a_2$ adrenergic receptor blocker that normally inhibit the release of the NE and 5-HT, thereby increasing active levels in the synapse. It also blocks post-synaptic 5-HT2 and 5-HT3 receptors—thereby enhance serotonergic neurotransmission while causing a low incidence of side effects

## Monoamine oxidase inhibitors (MAOI)

- The discovery of MAOIs resulted from a search for derivatives of isoniazid which has an anti-tubercular activity.




Isoniazide
Antitubercular but too polar

Iproniazide
Antitubercular but CNS stimulant
Which later shown to be MAOI
resulting in ↑ NE & 5-HT

New antidepressant introduced but withdrawn due to liver toxicity, however, increased interest on hydrazines and hydrazides for antidepressants

$H_2N—NH_2$
hydrazines

Thus MAOIs based on the hydrazine molecule have been extensively studied. Hydrazine, itself, has no MAOI activity

## General structure:

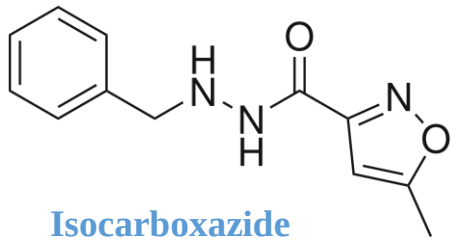
- Must have a free amino at one end to be active; a protonatable terminal N is necessary; those without a terminal N are prodrugs and must be bioactivated
- Must have at least one free hydrogen on each nitrogen
- Adding an alkyl group to one nitrogen of hydrazine confers MAOI activity: Ethyl is the most potent of the series methyl, ethyl, propyl, etc. Branching with a methyl group does not affect potency

## Ring Addition

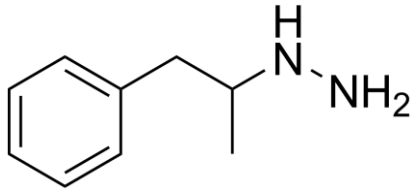
- Adding a phenyl ring produces a compound with no MAOI activity
- Adding a benzyl ring confers good activity, adding a phenethyl (phenyl ethyl) ring is even more potent
- More closely approximates norepinephrine, serotonin and dopamine, etc

## Disubstitution

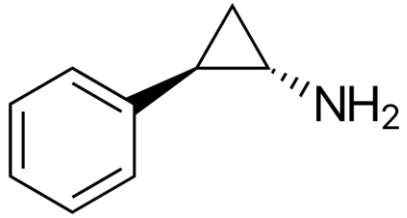
N,N disubstitution on one end decreases, or loses, potency



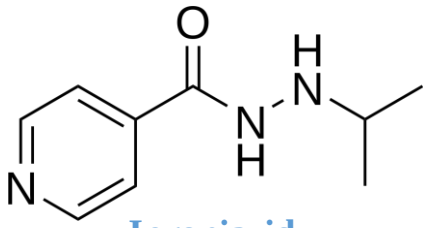

Isocarboxazide



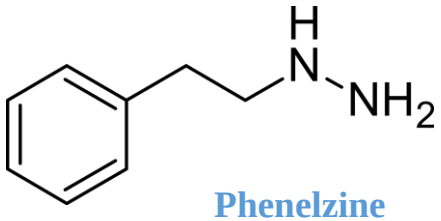

Pheniprazine



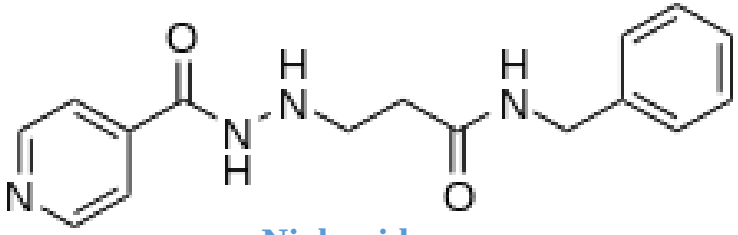

Tranylcypromine




Iproniazid



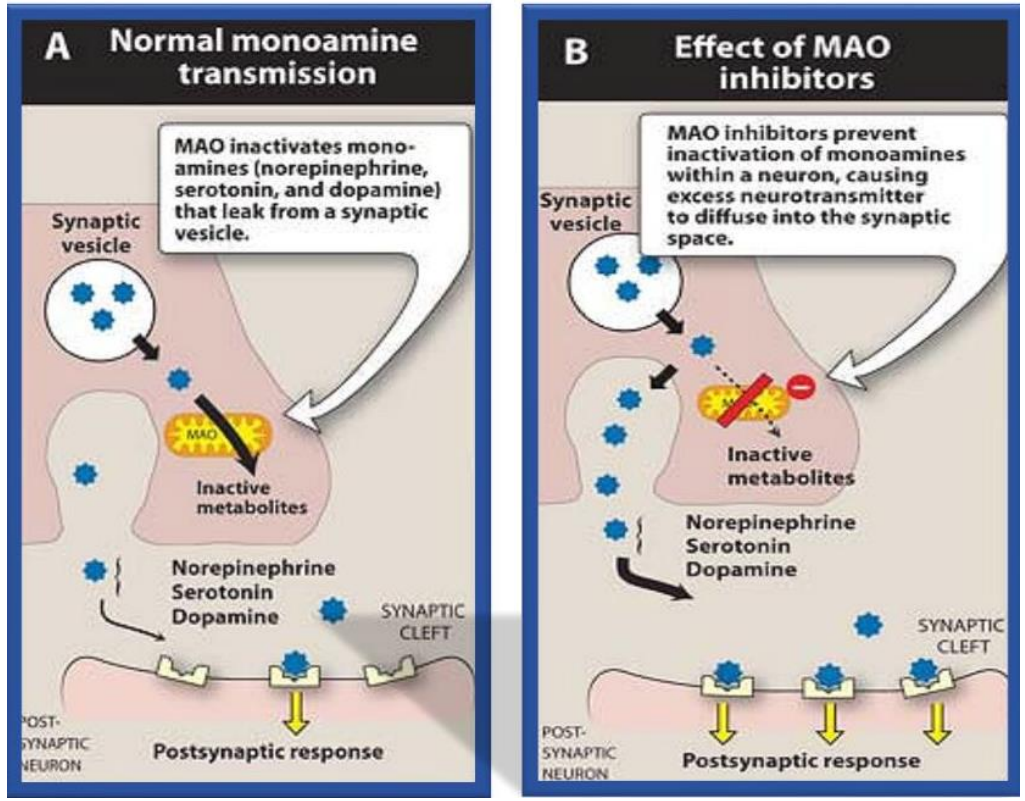

Phenelzine




Nialamide

## Mode of action:

- MAO is a mitochondrial enzyme found in nerve and other tissues. Monoamine oxidase breaks down norepinephrine, serotonin, and dopamine. When monoamine oxidase is inhibited, norepinephrine, serotonin, and dopamine are not broken down, increasing the concentration of all three neurotransmitters in the brain.
- MAOIs may reversibly or irreversibly inactivate the enzymes by making stable complexes with the enzymes,permitting neurotransmitter molecules to escape degradation and accumulate within synaptic cleft.




- This may cause activation of nor epinephrine and serotonin receptors responsible for anti depressant action

## Therapeutic uses

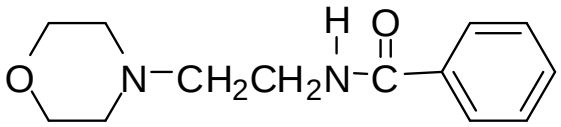
- Indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety
- Treatment of phobic states
- Treatment of atypical depression (labile mood, rejection sensitivity, and appetite disorders)
- Considered to be last-line agents in treatment because of their risk for drug-drug and drug-food interaction

## Adverse effects

1. Drug-food and drug-drug interactions:
   - Individuals receiving a MAOI are unable to degrade tyramine causing the release of large amounts of stored catecholamines from nerve terminals, resulting in "hypertensive crisis," (headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, stroke)
   - Patients must be educated to avoid tyramine-containing foods
2. Drowsiness
3. Orthostatic hypotension

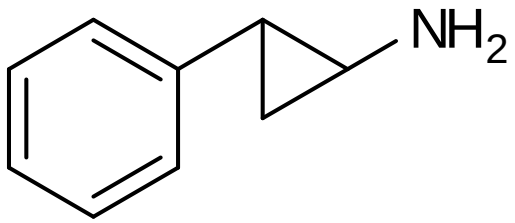
## Competitive MAOIs

- The present clinically useful irreversible MAOIs are mechanism-based as they form reactants that covalently bond the enzyme or its cofactor
- Thus they may continue their action up to 2 weeks after administration is discontinued
- The harmala alkaloid harmaline and harmine are competitive inhibitors of MAO and are CNS stimulants
- Moclobemide has received considerable attention. It is an effective antidepressant without producing hypotensive crisis which is a reversible inhibitor of MAO-A and permits metabolism of dietary tyramine, however, caution is still needed to avoid excessive intake (of cheddar cheese, feva beans)



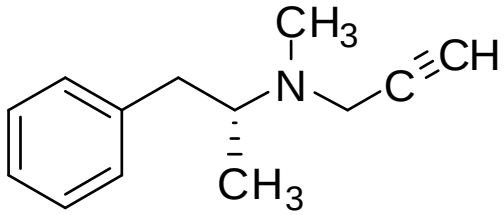
Moclobemide

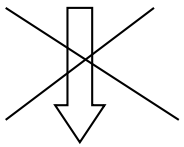
## Miscellaneous MAOIs

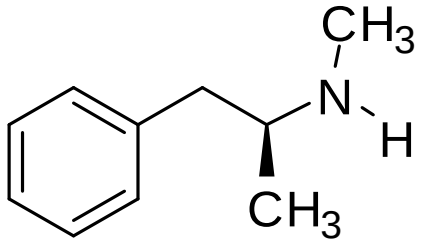



### Tranylcypromine

- The distance from the phenyl to the amine is closer to norepinephrine
- *The cyclopropyl group is very strained (reactive) and alkylates the enzyme*
- The *trans* isomer is more potent than the *cis* isomer
- The ring is more unstable and binds the enzyme better






### (-)-Selegiline

- Has an acetylene functional group that is unstable
- *Results in covalent bond to the enzyme*
- Part of its metabolic fate is N-dealkylation to methamphetamine
- Selegiline is the (–) isomer and so it forms (–) methamphetamine not the active (+) form as shown
- Selective MAO-B irreversible inhibitor (at lower doses)